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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/894,547	06/28/2001	William R. Wagner	214001-00810-1	6231
7590 03/08/2007 Debra Z. Anderson Eckert Seamans Cherin & Mellott, LLC 44th Floor 600 Grant Street Pittsburgh, PA 15219			EXAMINER POPA, ILEANA	
			ART UNIT 1633	PAPER NUMBER
SHORTENED STATUTORY PERIOD OF RESPONSE		MAIL DATE	DELIVERY MODE	
3 MONTHS		03/08/2007	PAPER	

**Please find below and/or attached an Office communication concerning this application or proceeding.**

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

**Office Action Summary**

Application No.

09/894,547

Applicant(s)

WAGNER ET AL.

Examiner

Ileana Popa

Art Unit

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 02 February 2007.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-3,5-19 and 21-29 is/are pending in the application.
- 4a) Of the above claim(s) 6,14-18,21 and 22 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-3,5,7-13,19 and 23-29 is/are rejected.
- 7) ☒ Claim(s) 11 and 28 is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)                                | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                       | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

### **DETAILED ACTION**

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 02/02/2007 has been entered.

### ***Election/Restrictions***

2. Upon further consideration the restriction requirement between the inventions of Groups I(i) and I(ii) as set forth in the Office action of 09/09/2005 is withdrawn, and Group I will be examined in its totality together with claims 23, 25, and 29, which are thereby included in Group I. Similarly, the species election requirement is withdrawn.

Claims 4 and 20 have been cancelled. Claims 6, 14-18, 21, and 22 have been withdrawn. Claims 1, 5, and 7 have been amended.

Claims 1-3, 5, 7-13, 19, 23-25, and 26-29 are under examination.

### ***Claim Objections***

3. Claim 11 objected to because of the following informalities: claim 11 recites "a solid" particulate. Since a particulate must be solid, the recitation is redundant. Appropriate correction is required.

It is noted that claim 12 depends from the objected claim 11.

4. Claim 28 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 28 recites "the method of claim 1, wherein the reactive group binds covalently". Since Applicant deleted recitations of ionic and non-covalent bonds and since claim 1 now recites only "wherein said reactive group binds covalently", claim 28 does not further limit claim 1 from which it is dependent.

***Claim Rejections - 35 USC § 112, second paragraph***

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter that the applicant regards as his invention.

6. Claim 29 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 29 discloses that the signaling molecule can be any molecule that will signal the recognition molecule "absent compatibility problems". It is not clear whether compatibility refers to compatibility with the host or compatibility with the recognition molecule.

***Claim Rejections - 35 USC § 112 - enablement***

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-3, 5, 7-12, 19, 24, and 26-28 are rejected under 35 U.S.C. 112, first paragraph, as being enabling only for a method for two-step delivery of a chemical or biological entity to cellular components of a blood vessel of a patient, wherein the cellular components are blood cells and endothelial cells and wherein the method comprises binding of NHS-biotin to blood cells or endothelial cells, followed by the attachment of a chemical/biological entity/avidin conjugate, for the reasons of record set forth in the prior Office actions of 11/23/2005 and 08/08/2006. It is noted that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Applicant argues that the claimed invention provides enablement for one of skill in the art to practice the invention without undue experimentation. Moreover, Applicant submits that his declaration under 37 CFR 1.132 filed on 02/02/2007 provides evidence and corroboration for this conclusion. In his declaration, Dr. Wagner asserts that not only one of skill in the art would be able to practice the claimed invention *in vitro* or *in situ* (i.e., isolated blood vessels), but also would be able to practice the invention *in vivo*, to deliver a chemical or biological entity to any target tissue or cell surface in a patient. Dr. Wagner submits that the paper attached to the declaration corroborates his

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assertion. The paper describes a method for the *in vivo* targeted delivery of fluorescent microspheres to balloon-injured or normal arterial surfaces by modifying the injured or normal arterial surface with NHS-PEG-biotin followed by NeutrAvidin-labeled fluorescent microspheres, wherein the NeutrAvidin-labeled fluorescent microspheres preferentially label the NHS-PEG-biotin-modified surfaces as compared to the unmodified ones. Dr. Wagner asserts that the same targeting strategy could be employed to deliver therapeutics to the tumor vasculature. Dr. Wagner concludes that the above paper clearly demonstrates the ability to provide site-specific recognition signals for the delivery of chemical and biological entities to healthy or damaged tissues in a patient, as recited in the independent claim 1, without encountering problems with endogenous biotin blocking the biotin-binding sites on streptavidin and accordingly, based on the disclosure in the specification and the results presented in the above paper, one of skill in the art would be able to practice the claimed invention without undue experimentation. Based on the evidence presented in the declaration, Applicant submits that the claimed invention provides more than adequate enablement for one of skill in the art to practice the invention in patients *in vivo* without undue experimentation and requests the withdrawal of the rejection.

Applicant's arguments and declaration are acknowledged however the claimed invention is not enabled to its full scope for the reasons of record set forth in the prior Office actions. The Examiner acknowledges that the invention is enabled for a method of two-step delivery of a chemical or biological entity to cellular components of a blood vessel of a patient, wherein the cellular components are blood cells and endothelial

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cells and wherein the method comprises binding of NHS-biotin to blood cells or endothelial, followed by the attachment of a chemical/biological entity/avidin conjugate. However, the specification does not teach, and the declaration does not demonstrate that the instant method (i.e., using any binding molecule comprising any reactive group, followed by attaching a recognition molecule having affinity for the binding molecule) can deliver a chemical or biological entity *in vivo* to any target tissue or cellular surface of a patient, as broadly claimed. The paper attached to the declaration does not support Dr. Wagner's assertion that one of skill in the art would be able to practice the claimed invention to its full scope, without undue experimentation, nor does the specification support such an assertion. The paper demonstrates that administering NHS-PEG-biotin (i.e., a binding molecule) to rabbit femoral artery through which the blood flow was interrupted by using aneurysm clips (i.e., administering the binding molecule *in situ* to isolated blood vessels) modifies the arterial endothelial cells such that the subsequent systemic administration of fluorescent microspheres coupled with avidin results in the preferential localization of these microspheres to the modified endothelial cells, as opposed to the unmodified endothelial cells in the arteries to which NHS-PEG-biotin was not administered. The paper also demonstrates that, in the case of balloon-injured arteries, the microspheres preferentially adhere to modified injured artery wall (i.e., the exposed basement membrane) as compared to the unmodified injured artery wall. The results above indicate that the endogenous biotin does not block the biotin-binding sites on streptavidin. It is noted that, since the artery was not flushed with saline, the surface of the remaining blood cells must necessarily have been

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modified because the NHS reactive group binds to any available amino group and therefore is not specific for a cell type or a specific protein. It is also noted that the bound microspheres were only detected by epi-fluorescence of explanted vessels placed in tissue culture dishes and cut lengthwise; this method cannot determine whether the fluorescent microspheres are able to be delivered beyond the endothelial layer or beyond the exposed basement membrane, therefore extrapolation from these results to general delivery to any tissue or cell is inappropriate. Therefore, the data above demonstrate that the claimed invention can be practiced *in vivo* only to deliver chemical or biological entities to the blood and endothelial cells (in the case of normal tissue) or to the blood cells and the basement membrane (in the case of injured vessels, wherein endothelial cells have been removed by the injury and the underlying basement membrane is exposed) of a patient. This is consistent with the scope of enablement.

Applicant argues that the specification provides more than adequate enablement for one of skill in the art to practice the invention in patients *in vivo* without undue experimentation. However, this argument is not found persuasive for the reasons of record set forth in the prior Office actions. Specifically, although Applicant claims targeted delivery to any tissue/cell surface, the instant method does not rely on any inherent feature present on the targeted surface and therefore the delivery cannot be specific unless the targeted tissue/cell surface is isolated. The delivery method is asserted by the as-filed application as being effective to deliver therapeutic or diagnostic agents to the tissue or cell surface. Essentially, the method as claimed, consists of attaching a molecule comprising a signaling molecule and a reactive group to a target

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tissue or cellular surface and introducing a chemical or biological entity expressing or comprising a recognition molecule to the target surface; the signaling and the recognition molecules bind, thereby attaching the entity to the target surface. The claims are very broad. The method, as claimed, does not rely on inherent feature present on the targeted surface; the target can be any tissue or cell surface. The molecule to be attached can be any biocompatible molecule comprising any group that will function as signaling molecule and any reactive group that would react under mild conditions with groups on the cell surface. Similarly, the entity to be delivered to the target broadly refers to a very broad genus of therapeutic or diagnostic agent, comprising pharmaceutical agents, vectors, nucleic acid sequences, cells or ultrasound contrasting agents. These are very broad ranges that include compounds with different mechanisms of action and pharmacokinetics, therefore the outcome of using these compounds is unpredictable. Even if signaling/recognition molecule pairs are well known in the art and one of skill in the art would be able to select a suitable pair of signaling/recognition molecules, one of skill in the art would not be able to specifically deliver the chemical or biological entity to the target tissue via the instant method in a patient as broadly claimed. The claimed invention is a method of specific delivery of a chemical/biological entity and therefore targeting to the desired tissue/cell surface is essential for the instant invention. It is noted that problems with the use of any signaling/recognition molecule pair for specific delivery *in vivo* exists. Apart from the *in vitro* delivery to endothelial cells in culture and delivery to endothelial cells in isolated arteries, wherein delivery takes place by using the biotin/avidin system, the specification

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fails to teach the use of any signaling/recognition system for specific delivery to any tissue/cell surface in a patient. The art clearly teaches that delivery problems to target tissues do exist there due to different barriers such as the endothelial cells of the vascular system, the basement membrane, and the extracellular matrix (see Garnett, of record). Moreover, the claims require that the binding molecule be covalently bound to the target tissue or cell surface, wherein the binding molecule comprises a reactive group such as NHS. As stated above, NHS is highly unspecific and it will covalently bind to the first encountered protein. Systemic delivery would mostly result in the NHS reacting with the amino groups of any encountered blood protein or cell, which are not necessarily the desired target. Local delivery would result in the NHS reacting with the amino groups of the extracellular matrix proteins and not necessarily in delivery to the targeted cell surface. One of skill in the art would readily recognize that such a method would result in the NHS-binding molecule being immobilized in the extracellular matrix or on blood cells/endothelial cells and not to the target cells, in the case of systemic administration, and therefore, one of skill in the art would readily recognize that such a method cannot result in the specific delivery to any cell or tissue, as claimed. The specification does not teach how to overcome any of the barriers above. Moreover, Applicant contemplates to deliver a variety of pharmaceutical agents, such as anti-mitotic or chemotherapeutic agents. Based on the facts above, one of skill in the art would not know how to deliver these agents to the targeted cells, without damaging the normal cells. Therefore, specification as filed does not provide any guidance or

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evidence that any signaling/recognition molecules pair can be used to deliver entities to any cell/tissue surface, as claimed.

Given the reasons above, the specification would need to describe examples that specifically address the use of each relevant signaling/recognition molecule pair for the targeted delivery of chemical or biological entities to any tissue or cell surface. In conclusion, the presently claimed invention only provides enough of a disclosure to allow for an artisan to use only NHS-biotin and a chemical or biological entity conjugated to avidin in a method to deliver the chemical or biological entity to cellular components of a blood vessel of a patient, wherein the cellular components are blood cells and endothelial cells.

### ***Claim Rejections - 35 USC § 102***

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

10. Claims 1, 3, 5, 7, 10-12, 19, 23, 24, 26, 28, and 29 are rejected under 35

U.S.C. 102(b) as being anticipated by Pouletty et al. (U.S. Patent No. 5,612,034).

Pouletty et al. teach a method of *in vivo* delivery (i.e., conditions tolerable *in vivo*) of agents of interest to blood cells and endothelial cells in patients by (i) injecting a first compound, wherein the first compound could be NHS-biotin (i.e., a binding molecule comprising an NHS reactive group and a biotin signaling molecule), wherein NHS is capable to form covalent bonds with the amino groups of the proteins on the blood or endothelial cell surface, and (ii) injecting a second compound comprising streptavidin or avidin (i.e., an entity having affinity for the signaling molecule) and the chemical or biological agent to be delivered (claims 1, 3, 5, 7, 19, 23, 24, 26, 28, and 29) (Abstract, column 1, lines 54-67, column 2, lines 1-5, column 3, lines 59-67, column 4, lines 24-33 and 56-65, column 5, lines 35-45, column 6, lines 13-23). Pouletty et al. teach that the agent of interest could be a synthetic drug such as an antibiotic (i.e., a chemical entity that is also a particulate), an anti-thrombotic or a chemotherapeutic agent (claims 10-12) (column 8, lines 43-60, column 9, lines 1-13). It is noted that, although Pouletty et al. disclose that any reactive group and any signaling molecule/recognition molecule pair is contemplated to be used in their method (column 3, lines 1-55, column 6, lines 13-23), this does not mean that these aspects of their inventions are enabled (see also above). Since Pouletty et al. teach all the limitations of the instant claims, the claimed invention is anticipated by the above-cited art.

11. Claims 1, 3, 5, 7, 10, 11, 13, 19, 23, 24, 28, and 29 are rejected under 35 U.S.C. 102(e) as being anticipated by Bridon et al. (PGPUB 2002/0018751).

Bridon et al. teach a method of *in vivo* delivery (i.e., conditions tolerable *in vivo*) of diagnostic imaging agents such as radioactive carbon (i.e., a particulate) to blood cells and endothelial cells in patients by (i) injecting a first compound, wherein the first compound could be NHS-biotin (i.e., a binding molecule comprising an NHS reactive group and a biotin signaling molecule), wherein NHS is capable to form covalent bonds with the amino groups of the proteins on the blood or endothelial cell surface, and (ii) injecting a second compound comprising streptavidin or avidin (i.e., an entity having affinity for the signaling molecule) and the diagnostic imaging agent to be delivered (Abstract, p. 1, paragraphs 0008-0012, p. 2, paragraphs 0019, 0020, 0025, 0028, 0030). Since Bridon et al. teach all the limitations of the instant claims, the claimed invention is anticipated by the above-cited art.

### ***Claim Rejections - 35 USC § 103***

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

13. Claims 1-3, 5, 7-12, 19, 24, and 26-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pouletty et al., in view of both Francis et al. (International Journal of Hematology, 1998, 68: 1-18, of record) and Kaiser et al. (Bioconjugate Chem., 1997, 8: 545-551, of record).

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The teachings of Pouletty et al. are applied as above for claims 1, 3, 5, 7, 10-12, 19, 24, 26, and 28. Pouletty et al. do not teach a polymer that masks adhesive information inherent to the tissue or cellular surface (claim 2), wherein the polymer is PEG (claims 8 and 9). Francis et al. teach that: (i) polyethylene glycol (PEG) modification is a well-established technique that has the capacity to solve or ameliorate many of the problems associated with protein pharmaceuticals, and (ii) PEGylation offers diverse advantages such as reducing toxicity and improving bioavailability (page 2, columns 1 and 2). It would have been obvious to one of skill in the art, at the time the invention was made, to PEGylate the binding molecule as taught by Francis et al., with a reasonable expectation of success. The motivation to do so is provided by Kaiser et al. who teach that, due to their antiadsorptive behavior, PEG chains decrease nonspecific binding (Abstract, page 545, column 2, second paragraph). One of skill in the art would have been expected to have a reasonable expectation of success in making and using such a composition because the art teaches that biotin-PEG conjugates comprising a reactive group can be successfully obtained and used.

With respect to the limitation of local delivery of the chemical or biological entity (claim 27), this is not innovative over the prior art. One of skill in the art would have been motivated to locally deliver the agent of interest to concentrate the agent at the desired site.

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

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14. Claims 1, 3, 5, 7, 10, 11, 13, 19, 23-25, 28, and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bridon et al., in view of Palasis et al. (U.S. Patent 6,369,039).

The teachings of Bridon et al. are applied as above to claims 1, 3, 5, 7, 10, 11, 13, 19, 23, 24, 28, and 29. Bridon et al. do not teach a microbubble ultrasound contrasting agent (claim 25). Palasis et al. teach targeted delivery of ultrasound contrasting agents, wherein the contrasting agent is a microbubble (Abstract, Summary of the invention, column 8, lines 22-32). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Bridon et al. by using the microbubble of Palasis et al. as an ultrasound contrasting agent, with a reasonable expectation of success. One of skill in the art would have been motivated to do so in order to obtain a visual display for evaluating the progression of a disease associated with blood and endothelial cell components. One of skill in the art would have been expected to have a reasonable expectation of success in making and using such a composition because the art teaches that such composition can be successfully made and used. Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

15. No claim is allowed. No claim is free of prior art.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ileana Popa whose telephone number is 571-272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Ileana Popa, PhD.

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